CTT Collaboration Independent Oversight Panel
Minutes of teleconference on Wednesday 28th February 2018

Attendees
Oversight Panel: Emily Banks, Michael Blastland, Stephen Evans, Peter Weissberg, Janet Wittes
CTT, Oxford: Colin Baigent, Kate Bird, Lisa Blackwell, Rory Collins, Kelly Davies, Heather Halls, Charlie Harper, Lisa Holland, David Preiss, Christina Reith, Enti Spata

Apologies
Oversight Panel: Robert Temple
CTT, Oxford: Jane Armitage, Jonathan Emberson, Boby Mihaylova

Agenda
1. Welcome and review and approval of last minutes from last TC
2. Declaration of Interests forms
3. Update on project progress
4. Funding

1. Welcome and review and approval of last minutes from last TC

The Panel was introduced to the wider CTT project team (including statisticians and research associates) who joined the call. The minutes from the last TC (which took place on Wednesday 11th October 2017) were agreed, and will be posted on the CTT website: www.cttcollaboration.org.

2. Declaration of Interests Forms

All Independent Oversight Panel members have completed a Declaration of Interests form, and all agreed that the text of such forms may be posted on the CTT website. However, the signed copies will be held on file in Oxford to protect against theft of electronic signatures/identity fraud.

3. Update on project progress

The CTT project to analyse all adverse events in eligible trials is progressing well. Randomized trials of statin therapy are eligible for this project if they fulfilled the original criteria for the CTT Collaboration analyses (no confounding with respect to the statin comparisons; ≥1000 participants with scheduled study treatment duration of at least 2 years). When the protocol was finalised in March 2016, this yielded 28 published trials, 27 of which are able to provide data (the one trial which is not able to provide information is the Primary prevention of cardiovascular disease with pravastatin in Japan [MEGA] Study, due to the data no longer being archived; note this was a relatively small, open-label study). At the time of the TC, data from 24 of these 27 trials had been received, with data from the remaining 3 trials expected in the near future.

The main challenges the research team are facing are (i) vast amount of data; (ii) substantial inter-trial heterogeneity between data format and types; (iii) some of the data being relatively 'dirty' (eg AE terms encompassing typographical errors). As an illustration of the immense size of the task at hand, to date, the research team have received:

- > 500 different datasets
- > 15 million records
- > 21,000 different variables
- ~ 700,000 AEs, with ~ 60,000 unique AE types

A 3-phase sequential approach has been adopted to assess and process this data as follows:

i. Review of methodological documentation
ii. Review of any tabular data
iii. Cleaning, processing and analysing individual participant data (IPD)

All phases of the project are subject to a rigorous documentation and tracking process.

The IPD phase is the most labour intensive, and requires a multidisciplinary team approach including clinicians, statisticians, research associates and administrative staff. In handling the IPD, received datasets are checked against marked up CRFs to identify pertinent missing data, and equally, if more datasets are received than anticipated, they are also assessed for pertinence. Any queries are resolved through contact with the trialists (where possible), or appropriate assumptions made. A 2 step approach is then used to address the issue of heterogeneity of IPD as follows:

(i) All data converted into a common format based on CDISC SDTM
(ii) All AE mapped to a common hierarchical coding system based on MedDRA methodology

A demonstration of the CTT MedDRA-based coding system was given. Essentially, this is an automated process for those AE terms which are direct MedDRA matches, with manual coding being deployed for terms that do not directly map. For the latter, the system is 'self-learning', so that unmapped terms only have to be mapped once, and will then be mapped consistently thereafter. The system has also been constructed to handle MedDRA multi-axiality, such that events terms default to the primary System Organ Class (SOC).

Once the data has all been processed and converted into a common format, the IPD tabular summaries will be produced and checked against previous trial publications, and again, any queries resolved through contact with the trialists, or appropriate assumptions made. Once all the IPD tabular summaries are agreed, the dataset will be ready for meta-analysis. One key methodological point that must be considered in this respect is the issue of multiple hypotheses testing (MHT). For example, MedDRA contains ~77,000 Lower Level Terms, and so representing analyses at this granular level of detail is likely inappropriate (with analysis at Higher Level Term or Higher Level Group Term thought to be likely preferable). The potential use of Standardised MedDRA Queries (SMQs) will also be explored, and all available MHT methodologies will be thoroughly assessed.

Given the scale and complexity of the project, preliminary results will not be expected until Q3/4 2018, or 2019 for more complex analyses such as incident diabetes, which also require processing and analyses of relevant laboratory and co-medication data.

The Independent Oversight Panel felt that substantial progress has been made given the huge amount and complexity of data, and felt that the methodology being devised for the project was appropriate and innovative. All agreed that making further details of the CTT approach available more widely would be beneficial. A methodological paper is already planned, and it was agreed that adding more details to the CTT website and making some video material aimed at the general public would be a good idea.

4. Funding

To date, the project has been supported by existing Clinical Trial Service Unit & Epidemiological Studies Unit funds. However, a project grant has been submitted to the British Heart Foundation, with results anticipated in April 2018.

5. Action Points and next meeting

- Oxford to post Panel Declaration of Interests Forms on CTT website
- Oxford to draft text to go on CTT website and start devising video material
- Agreed that the next meeting should take place in approximately 6 months' time; a Doodle poll to this effect will be sent to Panel members